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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/071,302	02/07/2002	Qinghong Yang	10752-016-999	1116
29585	7590	12/03/2003	EXAMINER	
GRAY CARY WARE & FREIDENRICH LLP			CLOW, LORI A	
153 TOWNSEND			ART UNIT	
SUITE 800			PAPER NUMBER	
SAN FRANCISCO, CA 94107			1631	

DATE MAILED: 12/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/071,302	YANG, QINGHONG	
	Examiner	Art Unit	
	Lori A. Clow, Ph.D.	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-26 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-26 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). ____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 1-26 are currently pending in the application.

Information Disclosure Statement

The Information Disclosure Statements filed 10 July 2002 and 19 September 2002 have been entered and considered. An initialed copy of the form PTO-1449 is enclosed with this action. Applicant is advised that a Search Report for a PCT is not considered a foreign patent document and is therefore improperly listed under "Foreign Patent Documents" in the IDS dated 10 July 2002. The examiner has altered the IDS so that the Search Reports listed are properly listed under "Other Documents" and reflect the mailing date of each.

Specification

The disclosure is objected to because of the following informalities:

(1) the specification contains blank spaces correlated to attorney docket numbers; for example. See page 30.

(2) the "Brief Description of the Figures" in the specification does not include a description of the several different views of the drawings. There is no description, for example of Figures 1A, 1B, 4A, 4B, 6A, 6B, or 6C. See 37 CFR 1.74 and MPEP 608.01.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-26 recite that branch migration is allowed to continue and dissociation into two duplexes results if there are no differences between the target and the reference nucleic acid. If there is a difference, a stabilized four-way complex is formed. In step (b) of claim 1, for example, “resolution of said four-way complex into two duplex nucleic acids” is indicated as meaning that the two nucleic acids are the same. However, in step (c) “detecting resolution of said four-way complex as an indication that said target polynucleotide sequence has a genotype that is the same as the known genotype” is confusing. It is suggested that the claim be amended to reflect that two duplexes are indicative of the nucleic acids being the same, as in step (c), and to distinguish this from formation of a four-way complex, which is indicative of a difference in the nucleic acid sequences.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8, 12-19, and 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yang et al. (US 6,653,079).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(c). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter

disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The present invention is directed to a method to determine the genotype at the site of a polymorphism comprising contacting a target polynucleotide with a reference polynucleotide under conditions in which the duplexes form a four-way complex, subjecting the four-way complex to branch migration conditions, wherein branch migration is impeded if the target sequence has a genotype that differs from the reference sequence, thereby forming a stabilized four-way complex, and wherein branch migration in the four-way complex is capable of continuing until complete strand exchange occurs if the target and reference share the same genotype, thereby resulting in the resolution of the four-way complex, and detecting the stabilized complex as an indication that the target has a genotype different from the reference or detecting two duplexes as an indication that target and reference are the same.

Yang et al. teach a method of detecting the presence or absence of a difference between two related nucleic acid sequences. The methods are sensitive enough to even detect the presence of a single nucleotide polymorphism (column 3, lines 1-8). In the method taught by

Yang et al. a target nucleic acid and a reference nucleic acid are contacted under conditions in which they are capable of forming a four-way nucleic acid complex with a branch structure that is capable of migration. Under these conditions, if the reference nucleic acid and the target nucleic acid are identical, branch migration is capable of going to completion resulting in complete stand exchange. If the reference nucleic acid and the target nucleic acid are different, branch migration cannot go to completion, resulting in a stable four-way complex. Detection of the complex identifies the presence of a difference in the nucleic acids (i.e. polymorphism). Detection of the complex can be achieved with molecules that specifically bind to the complex, by gel electrophoresis, or by specific isolation of the four-way complex (column 3, lines 17-36), as in claims 1, 12, 23, and 25 of the instant application.

Yang et al. also teach that the polynucleotides of the invention can be derivitized or modified (column 6, lines 37-40). Furthermore, two nucleic acid sequences are “related” when they are identical to each other or would be identical if not for some difference in the sequence, such as a substitution, deletion, or insertion of any single or a series of nucleotides within the sequence. Furthermore the differences could be a polymorphism (column 10, line 19). It would have been prima facie obvious to one of ordinary skill in the art to mutate the reference or target or both based upon the motivation above by Yang. Furthermore, Yang states that the present invention is universal and permits detection of any difference in two related sequences, regardless of whether such a difference is known a priori. Those differences include any mutation within a nucleic acid sequence, e.g. a single or multiple base substitution or polymorphism, a deletion, or insertion. These methods are ideally suited for mutation pre-screening and genotyping, particularly the identification of single nucleotide polymorphisms

(column 9, lines 39-56). Therefore it would have been prima facie obvious to have mutations that were single or multiple, as recited in claims 2-8, 14-19, and 24, as motivated by Yang et al. definition of the universal nature of the invention and the definition of “related” sequences above.

Claims 9, 20, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yang et al. (US 6,653,079) as applied to the claims 1-8, 12-19, 23-25 above, in view of Wu et al. (Nucleic Acids Research (1998) Vol. 26, pages 5432-5440).

While Yang et al. teach a method of detecting the presence or absence of a difference between two related nucleic acid sequences, as described above, Yang et al. do not teach the specific limitation of duplexes containing GC-rich sequences, as in claims 9, 20, and 26. However, Wu et al. do teach this limitation.

Wu et al. teach that an introduction of a GC-rich sequence, through PCR using GC-clamped primers, not only prevent fragments from melting completely, but also alters the melting characteristics of the fragment (page 5432, column 2). As admitted by the specification on page 3, this technique was well known in the art at the time of the invention. It would have been obvious to one of ordinary skill in the art at the time of the invention to modify melting temperature using well-known techniques such as those taught by Wu for the duplexes of the instant invention, as motivated by the desired stability of primers in a PCR reaction when GC-rich sequences are added.

Claims 10, 21, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yang et al. (US 6,653,079) as applied to the claims 1-8, 12-19, 23-25 above, in view of Kumar et al (Nucleic Acids Research (1998) Vol. 26, pages 831-838).

Yang et al. do not specifically teach the specific limitation of duplexes with minor groove binding motifs, as in claims 10, 21 and 26. However, Kumar et al. do teach this limitation.

Kumar et al. show that a duplex consisting of oligodeoxyribonucleotide 5'-TGATTATCTG-3' conjugated at the 5'-end to CDPI₃ (a minor groove binding moiety) and its complementary strand to an unmodified control duplex of the same sequence using nuclear magnetic resonance had a melting temperature that was 30 degrees C higher compared to the unmodified control duplex (page 831, abstract). Thus it would have been prima facie obvious to one of skill in the art at the time of the invention to use the technique of Kumar to alter melting temperature of the duplex in the invention of Yang as motivated by the desire for a more stable duplex (see abstract, page 831).

Claims 11, 22, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yang et al. (US 6,653,079) as applied to the claims 1-8, 12-19, 23-25 above, in view of Giesen et al. (Nucleic Acids Research (1998) Vol. 26, pages 5004-5006).

Yang et al. do not teach the specific limitation of duplexes with PNAs, as in claims 11, 22, and 26. However, Giesen et al. do teach this limitation.

Giesen et al. teach that the two strands of a PNA/DNA hybrid lack the electrostatic repulsion as observed in DNA/DNA duplexes, giving rise to virtually ionic strength independent thermal stability (T_m). Furthermore, PNA/DNA duplexes generally have a higher melting

temperature than the corresponding DNA/DNA duplexes (page 5004, column 1). Therefore, it would have been prima facie obvious at the time of the invention to use a PNA/DNA hybrid of Giesen in the instant invention to detect genotypes at the site of polymorphism, as motivated by the attainment of higher affinity and specificity of the PNA complexes (see abstract, page 5004).

Claims 1-8, 12-19, and 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,232,104 (Lishanski et al.).

Lishanski et al. teach universal method to detect any difference in two related nucleic acid sequences, whether or not such a difference is known. Differences include any mutation such as a single base mutation, deletion, or insertion that can be defined by a pair of primers for conducting the polymerase chain reaction (column 5). The invention involves formation of a four-strand cruciform DNA structure or complex. Partial duplexes are formed by amplification using three different primers in PCR and allowing products to anneal. The complex dissociates into normal duplex structures by strand exchange by means of branch migration when the double stranded portions of each partial duplex are identical. However, if there is a difference between the two double stranded portions, the complex does not dissociate and can be detected as an indication of the presence of a difference between the nucleic acids (column 5). While Lishanski et al. do not teach the specific mutations to the duplexes, as recited in the above claims, it would have been prima facie obvious to one of ordinary skill in the art to mutate one or the other or both of the target and reference at various places along the duplex, as motivated by Lishanski et al. at column 7 and 8: "the reference nucleic acid is a sequence that is related to the target nucleic

acid in that the two are identical except for the presence of a difference, such as a mutation (column 7). A mutation may include a polymorphism (column 8)".

Claims 9, 20, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,232,104 (Lishanski et al.), as applied to claims 1-8, 12-19, 23-25 above, in view of Wu et al. (Nucleic Acids Research (1998) Vol. 26, pages 5432-5440).

While Lishanski et al. teach a method of detecting the presence or absence of a difference between two related nucleic acid sequences, as described above, Lishanski et al. do not teach the specific limitation of duplexes containing GC-rich sequences, as in claims 9, 20, and 26.

However, Wu et al. do teach this limitation.

Wu et al. teach that an introduction of a GC-rich sequence, through PCR using GC-clamped primers, not only prevent fragments from melting completely, but also alters the melting characteristics of the fragment (page 5432, column 2). As admitted by the specification on page 3, this technique was well known in the art at the time of the invention. It would have been obvious to one of ordinary skill in the art at the time of the invention to modify melting temperature using well-known techniques such as those taught by Wu for the duplexes of the instant invention, as motivated by the desired stability of primers when GC-rich sequences are added.

Claims 10, 21, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,232,104 (Lishanski et al.), as applied to claims 1-8, 12-19, 23-25 above, in view of Kumar et al (Nucleic Acids Research (1998) Vol. 26, pages 831-838).

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Claims 11, 22, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,232,104 (Lishanski et al.), as applied to claims 1-8, 12-19, 23-25 above, in view of Giesen et al. (Nucleic Acids Research (1998) Vol. 26, pages 5004-5006).

Lishanski et al. do not teach the specific limitation of duplexes with PNAs in claims 11, 22, and 26. However, Giesen et al. do teach this limitation.

Giesen et al. teach that the two strands of a PNA/DNA hybrid lack the electrostatic repulsion as observed in DNA/DNA duplexes, giving rise to virtually ionic strength independent thermal

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stability (T_m). Furthermore, PNA/DNA duplexes generally have a higher melting temperature than the corresponding DNA/DNA duplexes (page 5004, column 1). Therefore, it would have been prima facie obvious at the time of the invention to use a PNA/DNA hybrid of Giesen in the instant invention to detect genotypes at the site of polymorphism as motivated by the attainment of higher affinity and specificity of the PNA complexes (see abstract, page 5004).

No Claims are Allowed.

Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703) 308-4242, or (703) 308-4028.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lori A. Clow, Ph.D., whose telephone number is (703) 306-5439. The examiner can normally be reached on Monday-Friday from 10 am to 6:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward, Ph.D., can be reached on (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Legal Instrument Examiner, Tina Plunkett, whose telephone number is (703) 305-3524, or to the Technical Center receptionist whose telephone number is (703) 308-0196.

Lori A. Clow
AU 1631

December 1, 2003

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